

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Thelin 100 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 100 mg sitaxentan sodium.

Excipients:

Also contains 166.3mg of lactose monohydrate.

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablet

Capsule shaped yellow-to-orange film-coated tablets, debossed with T-100 on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of patients with pulmonary arterial hypertension classified as WHO functional class III, to improve exercise capacity. Efficacy has been shown in primary pulmonary hypertension and in pulmonary hypertension associated with connective tissue disease.

4.2 Posology and method of administration

Treatment should only be initiated and monitored by a physician experienced in the treatment of pulmonary arterial hypertension.

Thelin is to be taken orally as a dose of 100 mg once daily. It may be taken with or without food and without regard to the time of day.

In the case of clinical deterioration despite Thelin treatment for at least 12 weeks, alternative therapies should be considered. However, a number of patients who showed no response by Week 12 of treatment with Thelin responded favourably by Week 24, so an additional 12 weeks of treatment may be considered.

Higher doses did not confer additional benefit sufficient to offset the increased risk of adverse reactions, particularly liver injury (see section 4.4).

Discontinuation of treatment

There is limited experience with abrupt discontinuation of sitaxentan sodium. No evidence for acute rebound has been observed.

Dosage in hepatic impairment:

Studies in patients with pre-existing liver impairment have not been conducted. Thelin is contraindicated in patients with elevated liver aminotransferases prior to initiation of treatment ($> 3 \times$ Upper Limit of Normal (ULN)) (see section 4.3).

Dosage in renal impairment:

No dose adjustment is required in patients with renal impairment.

Use in children and adolescents (< 18 years).

Thelin is not recommended for use in children and adolescents below 18 years due to a lack of data on safety and efficacy.

Elderly patients:

No dosage adjustment is needed in patients over the age of 65 years.

Use in patients using other medicines:

The efficacy and safety of Thelin co-administration with other treatments for pulmonary arterial hypertension (e.g. epoprostenol, sildenafil, iloprost) has not been studied in controlled clinical trials. Therefore, caution is recommended in case of co-administration.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Mild to severe hepatic impairment (Child-Pugh Class A-C).

Elevated aminotransferases prior to initiation of treatment (aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) > 3 x ULN).

Concomitant administration with ciclosporin A (see section 4.5).

Lactation (see section 4.6).

4.4 Special warnings and precautions for use

No data are available with Thelin in patients with pulmonary hypertension associated with pulmonary veno-occlusive disease. However, cases of life threatening pulmonary oedema have been reported with vasodilators (mainly prostacyclin) when used in those patients. Consequently, should signs of pulmonary oedema occur when Thelin is administered in patients with pulmonary hypertension, the possibility of associated veno-occlusive disease should be considered.

The efficacy of Thelin as monotherapy has not been established in patients with NYHA/WHO Functional Class IV pulmonary arterial hypertension. Transfer to a therapy that is recommended at the severe stage of the disease (e.g. epoprostenol) should be considered if the clinical condition deteriorates (see section 4.2).

Liver function:

Liver function abnormalities have been associated with pulmonary arterial hypertension. Endothelin receptor antagonists, as a class, have been associated with liver function abnormalities.

Elevations of AST and/or ALT associated with Thelin occur both early and late in treatment, usually progress slowly, and are typically asymptomatic. During clinical trials, these changes were usually reversible when monitoring and discontinuation guidelines were followed. Liver aminotransferase elevations may reverse spontaneously while continuing treatment with sitaxentan sodium.

Because treatment-associated elevations of AST and/or ALT are a marker for potential serious liver injury, liver aminotransferase levels must be measured prior to initiation of treatment and subsequently at monthly intervals. If AST and/or ALT are above 3 x ULN prior to initiation of therapy, use of Thelin is contraindicated (see section 4.3).

Recommendations in case of treatment-emergent ALT/AST elevations:

If ALT/AST measurements rise to the following levels then changes to the monitoring or treatment are given

> 3 and $\leq 5 \times \text{ULN}$ Confirm by another liver test within 2 weeks. If confirmed, continue to monitor aminotransferases at least every 2 weeks. If the aminotransferase levels return to pre-treatment values, return to monthly liver testing.

> 5 $\times \text{ULN}$ If aminotransferase levels increase to above 5 $\times \text{ULN}$, stop treatment and monitor aminotransferase levels at least every 2 weeks until levels have normalised. If the aminotransferase levels return to pre-treatment values, consider reintroducing Thelin according to the conditions described below.

If liver transferase elevations are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, anorexia, fever, abdominal pain, jaundice, or unusual lethargy or fatigue) or increases in total bilirubin above 2 $\times \text{ULN}$, treatment should be stopped and re-introduction of Thelin is not to be considered.

Re-introduction of treatment:

Re-introduction of treatment with Thelin should only be considered if the potential benefits of treatment with Thelin outweigh the potential risks and when liver aminotransferase levels are within pre-treatment values. The advice of a hepatologist is recommended. Re-introduction must follow the guidelines detailed in section 4.2. Aminotransferase levels must then be checked within 3 days after re-introduction, then again after a further 2 weeks, and thereafter according to the recommendations above.

Pre-existing liver impairment

Studies in patients with pre-existing liver impairment have not been conducted. Thelin is contraindicated in patients with elevated liver aminotransferases prior to initiation of treatment (> 3 $\times \text{ULN}$, see section 4.3).

Haemoglobin concentration

Treatment with Thelin was associated with a dose-related decrease in haemoglobin (see section 4.8). Most of this decrease of haemoglobin concentration was detected during the first few weeks of treatment and haemoglobin levels stabilized by 4 weeks of Thelin treatment. It is recommended that haemoglobin concentrations be checked prior to treatment, after 1 and 3 months, and every 3 months thereafter. If a marked decrease in haemoglobin concentration occurs, further evaluation should be undertaken to determine the cause and need for specific treatment.

Bleeding

There is an increased risk of bleeding with Thelin, mainly in the form of epistaxis and gingival bleeding.

Vitamin K antagonists

Thelin increases the plasma levels of Vitamin K antagonists such as warfarin, acenocoumarol and fenprocoumon (see section 4.5).

Drugs which inhibit OATP

The extent of interaction with potent OATP inhibitors (e.g. some statins, proteinase inhibitors, tuberculostatics) is unknown. As this could result in raised plasma levels of sitaxentan sodium, patients in need of the combination should be closely monitored for adverse events related to sitaxentan sodium.

Oral contraceptive agents

Thelin use results in increased oestrogen exposure when given concomitantly with oral contraceptive agents (see Section 4.5). Therefore, especially in women who smoke, there is an increased risk for thromboembolism. Given a theoretical higher risk for thromboembolism, traditional concomitant use of vitamin K antagonists is of special importance.

Pregnancy

Due to possible teratogenicity, the treatment must not be initiated in women of child-bearing potential unless they practice reliable contraception. If necessary, pregnancy testing should be undertaken (see Section 4.6).

Excipients

Thelin tablets contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

In vitro data indicate that sitaxentan sodium is an inhibitor of CYP2C9 and, to a lesser extent, of CYP2C19, CYP3A4/5 and CYP 2C8. Plasma concentrations of drugs principally metabolized by these isoenzymes, particularly CYP2C9 may be increased during sitaxentan sodium co-administration. Co-administration with drugs metabolized by CYP2C19 or CYP3A4/5 is not expected to result in clinically significant drug interactions. Based on a similar study with digoxin, Thelin does not affect the p-glycoprotein transporter.

Sitaxentan sodium is metabolized by CYP2C9 and CYP3A4/5. Administration of Thelin with CYP2C9 and CYP2C19 inhibitors is not expected to result in clinically significant drug interactions. Based on a study with ciclosporin it was postulated that sitaxentan sodium is a substrate of OATP transporter proteins.

Effects of Thelin on other medicinal products

Warfarin (vitamin K antagonist, substrate of CYP2C9): Concomitant treatment with Thelin resulted in a 2.4 fold increase in S-Warfarin exposure. Subjects receiving warfarin achieve therapeutic anticoagulation (International Normalised Ratio (INR) target) with lower doses of the anticoagulant in the presence of sitaxentan sodium. It is expected that a similar increase in anticoagulant effect will be seen with warfarin analogues, including acenocoumarol, fenprocoumon and fluindione. When initiating vitamin K antagonist therapy in a patient taking sitaxentan sodium, it is recommended to start at the lowest available dose of the vitamin K antagonist. In patients already taking such medication, it is recommended that the vitamin K antagonist be reduced when starting sitaxentan sodium. In all cases, INR should be monitored on a regular schedule. Increases in the vitamin K antagonist should be done in small increments to reach an appropriate target INR.

Omeprazole (substrate of CYP2C19): Concomitant administration of Thelin with omeprazole increased the omeprazole AUC₀₋₂₄ by 30%; C_{max} was unchanged. The change in AUC was not considered clinically significant.

Nelfinavir (substrate of CYP2C19 and CYP3A4/5): Concomitant administration of Thelin with nelfinavir did not clinically significant change the clearance of nelfinavir. The clearance of nelfinavir was not clinically significant changed in one subject that was classified as a CYP2C19 poor metabolizer.

Ciclosporin A (substrate of CYP3A4/5): Thelin coadministered with ciclosporin A did not change the clearance of ciclosporin A. However, because of its effect on Thelin pharmacokinetics, use of Thelin in patients receiving ciclosporin A is contraindicated (see section 4.3).

Ketoconazole (substrate of CYP3A4/5): Co-administration of Thelin with ketoconazole did not clinically significant change the clearance of ketoconazole.

Nifedipine (substrate of CYP3A4/5): The clearance of nifedipine was not clinically significantly changed when given concomitantly with sitaxentan sodium. This was tested for low-dose nifedipine only. Therefore, at higher nifedipine dosages an increase in exposure cannot be excluded.

Oral contraceptives: Concomitant administration of Thelin and Ortho-Novum 1/35 (1 mg norethindrone/ 0.035 mg ethinyl estradiol) resulted in increases in exposure to ethinyl estradiol (substrate of CYP3A4/5) and norethindrone (CYP3A4/5) of 59 % and 47%, respectively. Thelin did not affect the anti-ovulatory activity of the oral contraceptive as assessed by plasma concentrations of FSH, LH, and progesterone.

Sildenafil (substrate of CYP3A4): A single dose of sildenafil 100 mg coadministered with Thelin increased C_{max} and AUC_{∞} of sildenafil by 18% and 28%, respectively. There was no change in C_{max} or AUC for the active metabolite, n-desmethylsildenafil. These changes in sildenafil plasma concentrations were not considered clinically significant. Interaction with sildenafil can be serious if hypotension occurs beyond a safe level. Study results suggest that the dose of sildenafil does not need to be adjusted during concomitant administration with sitaxentan sodium.

Digoxin (Substrate of p-Glycoprotein): Concomitant administration of Thelin did not alter the pharmacokinetics of digoxin indicating no effect on the p-glycoprotein transporter.

No clinical interaction study was performed with a substrate of CYP 2C8. Therefore an interaction with such a drug cannot be excluded.

Effects of other medicinal products on sitaxentan sodium

Fluconazole (potent inhibitor of CYP2C19 and CYP2C9, and a moderate inhibitor of CYP3A4/5): Coadministration Thelin and fluconazole had no effect on the clearance of sitaxentan sodium.

Ketoconazole, and nelfinavir (potent inhibitor of CYP3A4/5): Concomitant administration of Thelin and ketoconazole or nelfinavir did not clinically significant change the clearance of sitaxentan sodium.

Ciclosporin A (Potent inhibitor of P-gp and OATP): Concomitant administration of Thelin (100 mg once daily) and ciclosporin A 3.5 mg/kg twice daily resulted in a 6-fold increase in the pre-dose concentrations of sitaxentan sodium. The mechanism for this interaction is not known. However, it is postulated that sitaxentan sodium is a substrate of the OATP transporter protein. Use of Thelin in patients receiving ciclosporin A is contraindicated (see section 4.3). Caution should be exercised when administering Thelin concurrently with other, more potent, OATP inhibitors. Co-administration of Thelin with the moderate OATP inhibitor nelfinavir did not result in increased Thelin plasma concentrations.

4.6 Pregnancy and lactation

Pregnancy

There are no human data regarding the use of sitaxentan sodium during pregnancy. Sitaxentan sodium caused teratogenicity in rats (see section 5.3). Potential effects in humans are unknown. Thelin should not be used during pregnancy unless clearly necessary i.e. in case no alternative treatment options are available.

Lactation

Sitaxentan sodium was detected in the plasma of breast fed pups from female rats treated with sitaxentan sodium, indicating that sitaxentan sodium was present in the breast milk. It is unknown whether or not sitaxentan sodium is excreted into human milk. Women should not breastfeed while using Thelin.

Women of child-bearing potential

Treatment must not be initiated in women of child-bearing potential unless they practice reliable contraception, due to possible teratogenicity. If necessary, pregnancy testing should be undertaken.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. A known undesirable effect is dizziness, which could influence the ability to drive or use machines.

4.8 Undesirable effects

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are reported as *very common* ($\geq 1/10$), *common* ($> 1/100$, $< 1/10$), *uncommon* ($> 1/1,000$, $\leq 1/100$), *rare* ($> 1/10,000$, $\leq 1/1,000$), and *very rare* ($\leq 1/10,000$). At the recommended dose during placebo-controlled trials in pulmonary arterial hypertension, the most common adverse drug reactions considered to be at least possibly related to Thelin treatment were headache in 15% of patients, and peripheral oedema and nasal congestion, each in 9% of patients. Adverse drug reactions that occurred in at least 2% of Thelin patients, at a rate greater than placebo, and that were considered to be at least possibly related to Thelin treatment included:

Metabolism and nutrition disorders: *Common*: Peripheral oedema.

Nervous system disorders: *Very common*: Headache. *Common*: Insomnia, dizziness.

Vascular disorders: *Common*: gingival bleeding.

Respiratory, thoracic, and mediastinal disorders: *Common*: Nasal congestion, epistaxis.

Gastrointestinal disorders: *Common*: Nausea, constipation, upper abdominal pain, vomiting, dyspepsia and diarrhoea.

Skin and subcutaneous tissue disorders: *Common*: Flushing.

Musculoskeletal and connective tissue disorders: *Common*: Muscle cramp.

General disorders and administration site conditions: *Common*: Fatigue.

Investigations: *Common*: INR increased, prothrombin (PT) prolonged.

Of these adverse drug reactions, those that occurred $\geq 2\%$ more frequently with Thelin than placebo were constipation, epistaxis, flushing, INR increased, insomnia, nasal congestion, nausea, peripheral oedema, and PT prolonged.

Laboratory Abnormalities

Increased Liver Aminotransferases (see section 4.4)

Elevations of AST and/or ALT are associated with sitaxentan sodium. In phase 2 and 3 oral studies in patients with PAH, elevations in ALT and/or AST > 3 ULN were observed in 5% of placebo-treated patients (N=155) and 7% of Thelin 100 mg-treated patients (N=887). Elevations in ALT values > 5 ULN were 4% (36/887) for sitaxentan 100 mg QD and 0.6% in the placebo group (1/155). Elevation of cases of symptomatic hepatitis has occurred in patients receiving Thelin 100 mg once daily. One fatal case has been reported with an initial dosage of sitaxentan of 600 mg/day.

Decreased Haemoglobin (see section 4.4)

The overall mean decrease in haemoglobin concentration for Thelin -treated patients was 0.5 g/dl (change to end of treatment). In placebo-controlled studies, marked decreases in haemoglobin ($> 15\%$ decrease from baseline with value $<$ lower limit of normal) were observed in 7% of patients treated with Thelin (N = 149) and 3% of placebo-treated patients (N = 155). A decrease in haemoglobin concentration by at least 1 g/dl was observed in 60% of patients treated with Thelin as compared to 32% of placebo-treated patients.

4.9 Overdose

There is no specific experience with the management of Thelin overdose. In the event of overdose, symptomatic and supportive measures should be employed.

During clinical trials, Thelin was given as a daily oral dose of 1000 mg/day for 7 days to healthy volunteers. The most common adverse effects at this dose were headache, nausea, and vomiting.

In an open-label hypertension study, 10 patients received 480 mg twice daily (approximately a 10-fold increase in daily dose compared to the MRHD) for up to 2 weeks. Headaches (some severe), peripheral oedema, and anaemias were the most common adverse events reported in these patients, none of which were considered serious.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antihypertensives, ATC code: C02KX03

Mechanism of action

Endothelin-1 (ET-1) is a potent vascular paracrine and autocrine peptide in the lung, and can also promote fibrosis, cell proliferation, cardiac hypertrophy, and remodelling and is pro-inflammatory. ET-1 concentrations are elevated in plasma and lung tissue of patients with pulmonary arterial hypertension, as well as other cardiovascular disorders and connective tissue diseases, including scleroderma, acute and chronic heart failure, myocardial ischaemia, systemic hypertension, and atherosclerosis, suggesting a pathogenic role of ET-1 in these diseases. In pulmonary arterial hypertension and heart failure, in the absence of endothelin receptor antagonism, elevated ET-1 concentrations are strongly correlated with the severity and prognosis of these diseases. Additionally, pulmonary arterial hypertension also is characterized by reduced nitric oxide activity.

ET-1 actions are mediated through endothelin A receptors (ETA), present on smooth muscle cells, and endothelin B receptors (ETB), present on endothelial cells. Predominant actions of ET-1 binding to ETA are vasoconstriction and vascular remodelling, while binding to ETB results in ET-1 clearance, and vasodilatory/ antiproliferative effects due in part to nitric oxide and prostacyclin release.

Thelin is a potent (K_i 0.35 nM) and highly selective ETA antagonist (approximately 6,500-fold more selective for ETA as compared to ETB).

Efficacy

Two randomized, double-blind, multi-centre, placebo-controlled trials were conducted to demonstrate efficacy. STRIDE-1, which included 178 patients, compared 2 oral doses of Thelin (100 mg once daily and 300 mg once daily) with placebo during 12 weeks of treatment. The 18 week STRIDE-2 trial, conducted in 246 patients, included 4 treatment arms: placebo once daily, Thelin 50 mg once daily, Thelin 100 mg once daily, and open-label bosentan twice daily (efficacy-rater blinded, administered according to the approved package insert).

Patients had moderate to severe (NYHA/WHO functional class II-IV) pulmonary arterial hypertension resulting from idiopathic pulmonary arterial hypertension (IPAH, also known as primary pulmonary hypertension), connective tissue disease (CTD), or congenital heart disease (CHD).

In these studies, the study medicine was added to patients' current therapy, which could have included a combination of digoxin, anticoagulants, diuretics, oxygen, and vasodilators (e.g., calcium channel blockers, ACE inhibitors). Patients with pre-existent hepatic disease and patients using non-conventional PAH treatments (e.g. iloprost) were excluded.

Sub-maximal exercise capacity was assessed by measuring distance walked in 6 minutes (6-minute walk test) at 12 weeks for STRIDE-1 and 18 weeks for STRIDE-2. In both trials, treatment with Thelin resulted in a significant increase in exercise capacity. The placebo-corrected increases in walk distance compared to baseline were 35 metres ($p=0.006$; ANCOVA) and 31 metres ($p<0.05$; ANCOVA), respectively.

Among patients with CTD, a statistically significant difference versus placebo was observed (37.73 metres, $p<0.05$).

A reduction in symptoms of pulmonary arterial hypertension was observed with Thelin treatment. In the STRIDE-1 trial, 59 (33%) of the 178 patients were classified at baseline as NYHA functional class II (mean baseline 6 minute walk distance 451 meters) and 117 (66%) as functional class III (mean baseline 6 minute walk distance 372 meters). Treatment with Thelin led to net improvement in NYHA functional class in 25% of patients (placebo 8%, $p<0.05$). In the STRIDE-2 trial 93 (38%) of the 246 patients were classified at baseline as NYHA functional class II (mean baseline 6 minute walk distance 370 meters) and 144 (59%) as functional class III (mean baseline 6 minute walk distance 322 meters). Treatment with Thelin led to net improvement in WHO functional class in 12% of patients (placebo -3%, $p<0.05$).

Haemodynamic parameters were assessed in STRIDE-1. Compared with placebo treatment, Thelin resulted in improvement ($p<0.05$) in cardiac index of $+0.3 \text{ L/min/m}^2$ (13%), in pulmonary vascular resistance of $-221 \text{ dynes*sec/cm}^5$ (22%), and in systemic vascular resistance of $-276 \text{ dynes*sec/cm}^5$ (16%) after 12 weeks of treatment. The reduction in mean pulmonary artery pressure of 3 mmHg (6%) was not statistically significant.

The effect of Thelin on the outcome of the disease is unknown.

Long-term Data

There are no studies to demonstrate beneficial effects on survival of treatment with sitaxentan sodium. However, patients completing STRIDE-2 were eligible to enrol in STRIDE-2X, a 1-year open-label study of Thelin 100 mg. A total of 145 patients were treated with Thelin 100 mg. In this total population, Kaplan-Meier estimates of survival were 96% for patients after 1 year of therapy with sitaxentan sodium. One-year survival estimates were similar in the subgroup of patients with PAH secondary to connective tissue disease for the Thelin treated group (98%). The estimates may have been influenced by the initiation of new or additional PAH therapies, which occurred in 24% of patients.

5.2 Pharmacokinetic properties

Absorption

Thelin is rapidly absorbed following oral administration. In PAH patients, peak plasma concentrations are generally achieved within 1-4 h. The absolute bioavailability of Thelin is between 70 and 100%. When administered with a high fat meal, the rate of absorption (C_{\max}) of Thelin was decreased by 43% and the T_{\max} delayed (2-fold increase) compared to fasted conditions, but the extent of absorption was the same.

Distribution

Thelin is more than 99% protein bound to plasma proteins, predominantly albumin. The degree of binding is independent of concentration in the clinically relevant range. Sitaxentan sodium does not penetrate into erythrocytes and does not appear to cross the blood-brain barrier.

Metabolism and Elimination

Following oral administration to healthy volunteers, sitaxentan sodium is highly metabolised. The most common metabolic products are at least 10 times less potent as ET_A antagonists than sitaxentan sodium in a standard *in vitro* test of activity. *In vitro*, sitaxentan sodium is metabolized by CYP2C9 and CYP3A4.

In vitro studies using human liver microsomes or primary hepatocytes show that sitaxentan sodium inhibits CYP2C9, and, to a lesser extent, CYP 2C8, CYP2C19 and CYP3A4/5.

Approximately 50-60% of an oral dose is excreted in the urine with the remainder eliminated in the faeces. Less than 1% of the dose is excreted as unchanged active ingredient. The terminal elimination half-life ($t_{1/2}$) is 10 hours. Steady state in volunteers is reached within about 6 days.

No unexpected accumulation in the plasma was observed after multiple dosing at the recommended dose of 100 mg once daily. However, at doses of 300 mg or higher, non-linear pharmacokinetics result in disproportionately higher plasma concentrations of sitaxentan sodium.

Special Populations

Based on results of the population pharmacokinetic analysis and pooled pharmacokinetic data over several studies, it was found that gender, race, and age do not clinically significantly affect the pharmacokinetics of sitaxentan sodium.

Liver Function Impairment

The influence of liver impairment on the pharmacokinetics of sitaxentan sodium has not been evaluated. Refer to section 4.3.

5.3 Preclinical safety data

In repeated-dose toxicity studies, dose-related liver changes (weight, centrilobular hypertrophy, occasionally necrosis), induction of hepatic drug metabolising enzymes and slightly decreased erythron parameters were seen in mice, rats and dogs. At high doses, dose-related increases in prothrombin time (PT) and activated partial thromboplastin time (APTT) were also seen, most prominently in rats, and coagulopathy (bleedings) in rats and dogs, but not mice. The significance of these findings for humans is unknown.

Testicular tubular atrophy was observed in rats, but not in mice or dogs. In the 26-week study, moderate to marked diffuse seminiferous tubular atrophy was present at a very low incidence, whereas in the 99-week study there was a dose-related, slightly increased incidence of minimal to mild focal atrophy at doses providing 29 to 94 times the human exposure.

Reproduction toxicity has been evaluated in rats only. Thelin did not affect fertility in males and females.

Thelin was teratogenic at the lowest tested dose in rats, corresponding to exposures more than 30 times the human exposure. Dose-dependent malformations of the head, mouth, face and large blood vessels occurred. A NOAEL has not been established. Administration of Thelin to female rats from late-pregnancy through lactation reduced pup survival, and caused testis tubular aplasia and delayed vaginal opening at the lowest exposure tested (17 – 45 times the human exposure). Large / abnormally shaped livers, a delay in auditory function development, a delay in preputial separation and a reduction in the number of embryonic implants occurred at higher maternal doses.

In vitro and *in vivo* tests on genetic toxicology did not provide any evidence for a clinically relevant genotoxic potential.

Thelin was not carcinogenic when administered to rats for 97-99 weeks or when administered to p53(+/-) transgenic mice for 6 months.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Cellulose, microcrystalline (E460)
Lactose monohydrate
Hypromellose (E464)
Sodium starch glycolate
Magnesium stearate (E470b)
Disodium phosphate, anhydrous (E339)
Ascorbyl palmitate (E304)
Disodium edetate
Monobasic sodium phosphate (E339)

Film coat:

Stearic acid (E570b)
Hypromellose (E464)
Cellulose, microcrystalline (E460)
Titanium dioxide (E171)
Yellow iron oxide dehydrate (E172)
Red iron oxide dehydrate (E172)
Talc (E553b)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

PVC/ACLAR/paper-backed aluminium blisters containing 14 tablets.
Cartons contain 14, 28, 56, or 84 tablets.
High-density polyethylene (HDPE) bottles containing 28 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Encysive (UK) Limited
Alder Castle House
10 Noble Street
London EC2V 7QJ
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/353/001
EU/1/06/353/002
EU/1/06/353/003
EU/1/06/353/004
EU/1/06/353/005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 August 2006

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicine is available on the European Medicines Agency (EMA) web site: <http://www.emea.europa.eu/>. There are also links to other websites about rare diseases and treatments.

ANNEX II

- A. MANUFACTURING AUTHORISATION HOLDER
RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OF THE MARKETING AUTHORISATION**

A. MANUFACTURING AUTHORISATION HOLDERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Encysive (UK) Limited
Regus House
Highbridge Industrial Estate
Oxford Road
Uxbridge UB8 1HR
United Kingdom

Patheon UK Limited
Kingfisher Drive
Covingham
Swindon, Wilts SN3 5BZ
United Kingdom

Polar Speed Distribution Ltd
Unit 8 Chartmoor Road
Leighton Buzzard
Bedfordshire LU7 4WG
United Kingdom

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OF THE MARKETING AUTHORISATION

• CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER

Medicinal product subject to restricted medical prescription. (See Annex I: Summary of Product Characteristics, section 4.2)

• CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

The MAH shall set up a surveillance programme to collect information on: the demographics of patients prescribed Thelin, any adverse reactions and reasons for discontinuation of Thelin. Details of such a surveillance programme should be agreed with the National Competent Authorities in each member state and put in place prior to marketing of the product.

The MAH must agree the details of a controlled distribution system with the National Competent Authorities and must implement such programme nationally to ensure that, prior to prescribing, all doctors who intend to prescribe Thelin are provided with a physician information pack containing the following:

- Product information
- Physician information about Thelin
- Patient information card
- Partner of patient information card

The physician information about Thelin should contain the following key elements:

- That Thelin is teratogenic
 - Use of effective contraception in women of child bearing age

- Possible interaction with oral contraceptives and increased risk of thromboembolism
- Need to advise female patients about teratogenicity, contraception, if necessary the need for pregnancy testing and what to do if they become pregnant
- Referral of patients who become pregnant to a physician specialised or experienced in teratology and its diagnosis for evaluation and advice
- That Thelin is hepatotoxic
 - Need for liver function tests prior to and during treatment
 - Contraindication in patients with pre-existing hepatic disease
 - Discontinue sitaxentan sodium immediately if liver enzymes rise above $5 \times \text{ULN}$
 - Need for close monitoring if liver enzymes measure > 3 and $\leq 5 \times \text{ULN}$, with repeat analysis every two weeks until values return to pre-treatment levels or discontinuation if analysis rises above $5 \times \text{ULN}$.
- That treatment with Thelin often causes a decrease in haemoglobin and related red cell parameters
 - Need for full blood count prior to use and monitoring at clinically appropriate intervals
- Effect of Thelin on bleeding
 - Interaction with warfarin and vitamin K antagonists leading to an increased INR
 - Need to decrease established dose of vitamin K antagonist upon starting sitaxentan therapy
 - Start vitamin K antagonists treatment at a reduced dose if already on sitaxentan sodium
 - Need for regular monitoring of INR
 - Be aware of the potential for haemorrhage and investigate as appropriate
 - Increased risk of epistaxis and gingival bleeding
- That there is an interaction with ciclosporin A which may lead to higher blood concentration of Thelin and hence an increased risk of adverse reactions.
- That the safety database of Thelin is limited and physicians are encouraged to enrol patients in a surveillance programme to increase knowledge about the incidence of important adverse drug reactions (ADRs). The surveillance programme should prompt doctors to report serious ADRs and certain selected ADRs as below immediately and other non-serious ADRs at three monthly intervals.

The information collected should include:

- Anonymised patient details – age, sex and aetiology of PAH
- Concomitant medications
- Reason for discontinuation
- ADRs
- All serious ADRs
- Increase in hepatic enzymes to $>3 \times \text{ULN}$
- Anaemia
- Haemorrhage
- Pregnancy and outcome
- Pulmonary oedema (associated with veno-occlusive disease)
- Suspected interactions
- Unexpected ADRs according to the SPC.

The Patient information card should include the following information

- That Thelin is teratogenic
- The need to ensure that women of child bearing age are using effective contraception and that patients should inform their doctors of any possibility of pregnancy before a new prescription is issued
- The need for female patients to contact their treating doctor immediately if they suspect that they might be pregnant.
- That Thelin is hepatotoxic and they will need to attend for regular blood tests

- The need to tell their doctor about any adverse events
- The need to tell their doctor that they are taking Thelin

Partner of patient information card should include the following information:

- That Thelin is teratogenic and that women of child bearing age must use effective contraception

OTHER CONDITIONS

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance, as described in version 1.1 presented in Module 1.8.1. of the Marketing Authorisation Application, is in place and functioning before and whilst the product is on the market.

Risk Management Plan

The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 5 of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the EMEA

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

BLISTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Thelin 100 mg film-coated tablets
Sitaxentan sodium

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 100 mg of sitaxentan sodium

3. LIST OF EXCIPIENTS

Contains lactose monohydrate

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets in blisters
28 film-coated tablets in blisters
56 film-coated tablets in blisters
84 film-coated tablets in blisters

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Store below 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE
--

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Encysive (UK) Limited
Alder Castle House
10 Noble Street
London EC2V 7QJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)
--

EU/1/06/353/001 (14 film-coated tablets in blisters)
EU/1/06/353/002 (28 film-coated tablets in blisters)
EU/1/06/353/003 (56 film-coated tablets in blisters)
EU/1/06/353/004 (84 film-coated tablets in blisters)

13. BATCH NUMBER

Lot: {number}

14. GENERAL CLASSIFICATION FOR SUPPLY
--

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Sitaxentan

To be written in braille at time of manufacture.

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
--

PVC/ACLAR/paper-backed aluminium blisters
--

1. NAME OF THE MEDICINAL PRODUCT

Thelin 100 mg film-coated tablets
Sitaxentan sodium

2. NAME OF THE MARKETING AUTHORISATION HOLDER
--

Encysive (UK) Limited

3. EXPIRY DATE

EXP: {MM/YYYY}

4. BATCH NUMBER

Lot: {number}

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

Bottle Label (fix-a form)

1. NAME OF THE MEDICINAL PRODUCT

Thelin 100 mg film-coated tablets
Sitaxentan sodium

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 100 mg of sitaxentan sodium

3. LIST OF EXCIPIENTS

Contains lactose monohydrate

4. PHARMACEUTICAL FORM AND CONTENTS

28 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Store below 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE
--

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Encysive (UK) Limited
Alder Castle House
10 Noble Street
London EC2V 7QJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)
--

EU/1/06/353/005

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY
--

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Sitaxentan

To be written in braille at time of manufacture.

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Thelin 100 mg film-coated tablets Sitaxentan sodium

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any side effect becomes serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Thelin is and what it is used for
2. Before you take Thelin
3. How to take Thelin
4. Possible side effects
5. How to store Thelin
6. Further information

1. WHAT THELIN IS AND WHAT IT IS USED FOR

Thelin is used to help lower blood pressure in the blood vessels when this pressure is raised in pulmonary arterial hypertension (PAH). Pulmonary arterial hypertension is the term used when the heart struggles to pump blood to the lungs. Thelin lowers the blood pressure by widening these vessels, so your heart can pump blood more effectively. This will make it easier for you to do more activities.

2. BEFORE YOU TAKE THELIN

Do not take Thelin:

- If you are **allergic** (hypersensitive) to sitaxentan sodium or any of the other ingredients in these tablets;
- If you have or have had a **serious liver problem**;
- If you have **raised levels of some liver enzymes** (detected by blood tests);
- If you are taking **Ciclosporin A** (used to treat psoriasis and rheumatoid arthritis, and to prevent rejection of liver or kidney transplants);
- If you are **breast-feeding** (please read the section ‘Pregnancy and breast-feeding’ below);
- If you are **a child or adolescent** under 18 years old.

Take special care with Thelin:

- If you could get **pregnant** or are pregnant (please read the section “Pregnancy and breast-feeding” below);
- If you **develop liver problems** or symptoms that might relate to the liver (see ‘Testing for liver problems’, below);
- If you are **taking or begin to take anticoagulants** (e.g. warfarin, acenocoumarol, fenprocoumon or fluindione) to prevent blood clots. The dose of these medicines may need to be adjusted by your doctor.
- If you are **taking a statin** (e.g. pravastatin or simvastatin).
- If you are taking a **high dose of nifedipine**.

If any of these apply to you, tell your doctor before you start taking Thelin.

The following two blood tests will be carried out before you first take Thelin and at intervals during treatment

Testing for liver problems

Thelin may affect your liver. Your doctor will take blood tests to check that your liver is working properly, before and during treatment with Sitaxentan sodium. It is important to have these tests every month during treatment, even if you do not have any symptoms at all.

If you notice any of these signs:

- feeling sick (nausea)
- being sick (vomiting)
- loss of appetite
- fever
- unusual tiredness
- pain in the stomach (abdominal pain)
- yellow colouring of the skin and eyes (jaundice)

Talk to your doctor immediately. These may be signs that your liver is not working properly.

Testing for anaemia

This blood test will be done before treatment, then one month and three months after you start taking Thelin tablets. Following this, the test will continue to be done every three months to check for anaemia (a reduced amount of red blood cells).

For your own safety, it is very important that you have regular blood tests.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes medicines you bought without a prescription, herbal remedies and vitamins.

These medicines may interfere with the effect of Thelin.

Do not take Thelin if you are taking Ciclosporin A.

Thelin should be used with caution if you are taking or begin to take Vitamin K antagonists (e.g. warfarin, acenocoumarol, fenprocoumon or fluindione).

Driving and using machines

Do not drive or use any tools or machines if you feel dizzy.

Pregnancy and breast-feeding

If you are able to get pregnant, you must use effective contraception while taking Thelin. Your doctor will advise you about suitable contraception. Your doctor may recommend monthly pregnancy tests while you are taking Thelin.

If you miss a period or think you may be pregnant, contact your doctor right away. He or she may want you to stop taking Thelin. **Tell your doctor at once if you are or plan to become pregnant in the near future.**

Do not breast-feed if you are taking this medicine, it is not known if it passes into breast milk.

Important information about some of the ingredients of Thelin

Thelin tablets contain lactose monohydrate. If you are intolerant to some sugars, contact your doctor before taking Thelin tablets.

3. HOW TO TAKE THELIN

The usual dose is a 100 mg tablet once a day.

Always take Thelin exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

- **Try to take the tablet at the same time each day** to help you remember. Swallow the tablet whole with water. It does not matter whether you take it with or without food.

Do not take more than one tablet each day. You may need to take Thelin for a month or two before feeling any effect.

If you take more Thelin than you should

If you realise you have taken more Thelin tablets than your doctor has recommended (or if someone else has taken some of your Thelin tablets), contact your doctor straight away. If you cannot reach your doctor, go to the nearest hospital and take the pack with you.

If you forget to take Thelin

If you miss a dose, take the missed dose as soon as you remember but **do not take two tablets in one day**.

If you stop taking Thelin

Talk to your doctor before stopping treatment.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Thelin can cause side effects, although not everybody gets them.

Very common side effects (likely to affect more than 1 in 10 patients):

- headache

Common side effects (likely to affect more than 1 in every 100 people):

- swelling in the arms and legs
- being unable to sleep
- blocked nose and nosebleeds
- bleeding from the gums
- feeling and/or being sick, difficulty in passing stools, stomach ache, indigestion and diarrhoea
- flushed
- cramp in muscles
- dizziness
- feeling tired
- your blood may take longer to clot.

Rare side effects (likely to affect less than 1 in 1000 people):

- Liver damage

For more details on liver problems, see 'Testing for liver problems' in section 2.

If any of the side effects become serious, or if you notice any other side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE THELIN

Keep out of the reach and sight of children.

Do not use Thelin after the expiry date which is stated on the blister pack, bottle or carton after EXP. The expiry date refers to the last day of that month.

Do not store above 25°C.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines you no longer require. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Thelin contains

- The **active substance** is sitaxentan sodium.

The other ingredients are:

- The **tablet core** contains cellulose, microcrystalline (E460), lactose monohydrate, hypromellose (E464), sodium starch glycolate, magnesium stearate (E470b), anhydrous disodium phosphate (E339), ascorbyl palmitate (E304), disodium edetate and monobasic sodium phosphate (E339).
- The **film-coat** contains stearic acid (E570b), hypromellose (E464), microcrystalline cellulose (E460), titanium dioxide (E171), yellow iron oxide dehydrate (E172), red iron oxide dehydrate (E172) and talc (E553b).

What Thelin tablets look like and contents of the pack

Thelin 100 mg film-coated tablets are yellow-to-orange, capsule-shaped tablets, marked with T-100 on one side.

Thelin comes in blister packs of 14, 28, 56, and 84 tablets and bottles of 28 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing authorisation holder:

Encysive (UK) Limited
Alder Castle House
10 Noble Street
London EC2V 7QJ
United Kingdom
Tel: +44 (0)208 610 6942

Manufacturer:

Encysive (UK) Limited Regus House Highbridge Industrial Estate Oxford Road Uxbridge UB8 1HR United Kingdom	Patheon UK Limited Kingfisher Drive Covingham Swindon, Wilts SN3 5BZ United Kingdom	Polar Speed Distribution Ltd Unit 8 Chartmoor Road Leighton Buzzard Bedfordshire LU7 4WG United Kingdom
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For any information about this medicinal product, please contact the Marketing Authorisation Holder.

This leaflet was last approved in

Detailed information on this medicine is available on the European Medicines Agency (EMA) web site: <http://www.ema.europa.eu/>. There are also links to other websites about rare diseases and treatments.